REMARKS

Claims 1-3 have been amended to more clearly claim the invention and new claims 20-28 have been added. In addition, withdrawn claims have been canceled solely as drawn to non-elected inventions. As a result of the present Amendment, Claims 1-3, 5, 17 and 20-28 are presented for further examination.

Support for the new claims is found in the specification and claims as filed, for example, on page 13: lines 24-27, page 13: line 29 through page 14: line 2, and page 14: line 8. The changes made to the claims by the current amendment, including ~~deletions~~ and additions, are shown herein with deletions designated with a strikethrough and additions underlined. No new matter has been added herewith.

Objections

The Examiner objected to Claims 1-3, pointing out that the recitation of agonists and antagonists was 1) directed to withdrawn inventions and 2) confusing and not enabled. Applicant has amended Claims 1-3 by omitting "antagonist", thereby removing both of these issues.

The Examiner objected to Claims 8, 9, and 18 for depending from canceled claims. Claims 8, 9, and 18 have been canceled to remove this issue.

Compliance under 35 U.S.C. §112, first paragraph

The Examiner has rejected Claims 1-3, 5 and 17 as failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. The Examiner noted that if bone resorption has already occurred, then it is not possible to delay the onset of said bone resorption. Claim 1 has therefore been amended to apply to an animal in which bone resorption has not yet occurred. Applicant believes that Claims 1-3, 5 and 17 are in compliance with 35 U.S.C. §112, first paragraph.

Compliance under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 8, 9, and 18 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention under 35 U.S.C.§112, second paragraph. Applicant has overcome this rejection by cancelling Claims 8, 9, and 18.

Compliance under 35 U.S.C. §102(e)

The Examiner has rejected Claims 1-3, 5, 8-9 and 17-18 as anticipated by Ke et al. (U.S. Pat. No.: 6,352,970. Claims 8-9 and 18 are cancelled by this amendment.

The claims have new been separated into three sets: (A) Claims 1-3, 5 and 17; (B) Claims 20-24 and (C) Claims 25-28. The patentability of each set of claims will be discussed in turn.

Claim Set A

Claim 1 has been amended to recite a method of delaying onset of bone resorption in an animal in which bone resorption has not yet occurred. Amended Claim 1 is not anticipated by Ke et al. which teaches a method of treatment in cases when bone loss has already occurred. As the Examiner notes on page 5, lines 9-11 of the Office Action, "Ke et al. teach that leptin is useful for treatment of conditions which present with low bone mass, including osteoporosis, bone fractures, osteotomy, etc. (see Ke et al. column 2, lines 30-45)". On page 6, lines 15-16 of the Office Action, the Examiner emphasizes: "Ke et al. is directed to treatment of a mammal in need of augmenting bone mass." The Applicant concurs with this portion of the Examiner's statement.[1]

Amended Claim 1 describes a method in which bone resorption has not yet occurred so there is no anticipation by Ke et al. Claims 2, 3, 5 and 17 depend from Claim 1 so they also are not anticipated by Ke et al. Applicant respectfully requests removal of the rejection under 35 U.S.C. §102(e).

Moreover, nothing in the Ke et al. reference even suggests that mammals that have not yet experienced bone resorption can have onset of such resorption delayed by administration of leptin.

Claim Set B

Claim 20 and its dependent claims relate to methods of treatment of animals that are already experiencing bone loss through resorption. The Examiner has equated animals in need of

[1] Applicant does not concur with the Examiner's implication that a mammal in need of augmenting bone mass is equivalent to a mammal "with bone loss, a.k.a. having bone resorption." This issue is addressed hereinbelow in connection with Claim Set B.

augmentation of bone mass with animals having bone resorption. However, this is clearly not the case. As stated previously, loss of bone mass can be due to either or both of two completely separate processes: (1) decreased production of bone mass mediated by osteoblasts or (2) increased bone resorption mediated by osteoclasts.[2] The Ke et al. reference is completely silent as to which of the two processes is being addressed.

In order for a reference to provide an *inherent* disclosure when the reference is silent about a recited characteristic, the missing descriptive matter must be *necessarily* present in the thing described in the reference. *See*, M.P.E.P. § 2131.01(III). Although Ke et al. does identify an animal which is in need of bone augmentation, it cannot be said to be inherent in Ke et al. that an animal with "excess bone resorption" is identified because Ke et al. does not state which of the two processes is to be treated. Indeed, animals with completely normal bone resorption can be in need of bone augmentation if they have decreased production of bone mass. As such, it is not a necessary result of Ke et al. that an animal with excess bone resorption is identified, as presently recited by the claims of Claim Set B. Accordingly, the Ke et al. reference does not anticipate Claim Set B.

Moreover, nothing in the Ke et al. reference even suggests that leptin has any effect on bone resorption. As such, Claim Set B is patentable over the Ke et al. reference.

Claim Set C

The Examiner indicated in the Office Action that claims limited to Paget's disease would be considered patentable over the art of record. Claims 24-28 (Claim Set C) is so-limited. Accordingly, allowance of Claim Set C is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, all of the outstanding objections and rejections have been overcome, and the application is believed to be in condition for allowance. Should the Examiner identify any issues which might impede such allowance, the examiner is respectfully requested to contact the undersigned at the telephone number appearing below.

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[2] These two processes are very well known by those having ordinary skill in the art. As an example, Applicant has attached a printout of http://www.nslc.wustl.edu/Research/HHMI/00fellows/melissa_calcaterra.html.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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REDUCED NUMBER OF STROMAL CELLS FOUND IN MURINE MODEL OF ACCELERATED SENESCENCE (SAM-P6). **Melissa Calcaterra**1, Matt Silva2. Biology Department, Washington University, St. Louis, MO1; Department of Orthopaedic Surgery, Washington University Medical School, St. Louis, MO2.

Bone is a dynamic tissue. Osteoclasts are responsible for the resorption of old bone, while osteoblasts induce the formation of new bone. When these two systems are not in equilibrium, changes in bone mineral density (BMD) occur. Decreased BMD can result from increased osteoclastogenesis or from decreased osteoblastogenesis and can lead to osteoporosis and increased fracture risk. SAM-P6 is a strain of mice with accelerated senescence and osteoporosis. We hypothesized that the reduced BMD found in this strain is due to impaired osteoblastogenesis. We tested this hypothesis by comparing bone marrow stromal cells from SAM-P6 mice to those of two control strains, AKR/J and SAM-R1 (the R1 and P6 strains were developed by the successive inbreeding of AKR/J mice). The R1 strain is an established control strain used in P6 experiments. However, we also wanted to investigate whether or not the AKR strain could be used as a suitable substitute for R1.

Two experiments were performed. In each experiment, mice were sacrificed, and bone marrow stromal cells were isolated from the tibias and femurs. The stromal cells were cultured in alpha-MEM with 10% FBS. After eight days, ascorbic acid and b-glycerophosphate were added to the media to induce osteoblast differentiation. Three-month old AKR and P6 male mice were used in the first experiment. The cells received supplemented media for 10 days before fixation and staining. The second experiment was conducted with 10-month old R1 and P6 male mice. Their cells received supplemented media for six days before fixation and staining.

A methylene blue assay was used to determine relative cell number in each culture. In addition, two techniques were used to determine the extent of osteoblast differentiation. Alkaline phosphatase (ALP) is an enzyme that, when expressed, indicates differentiation of stromal cells into osteoblasts. ALP was measured using both a biochemical assay and a cytological stain. Assay results were obtained by spectrophotometer readings. The extent of staining was determined by imaging the cell culture plates and, using computer software, measuring the percent area of the plate that was stained.

The methylene blue assay results of both experiments (AKR v. P6 and R1 v. P6) indicate a reduced number of stromal cells in the P6 strain when compared to the respective control strain. ALP analysis of both experiments suggests that there is more ALP activity per cell number in the P6 strain than in the respective control strain. However, the two experiments differ when comparing the total number of ALP-positive cells in culture. AKR v. P6 data indicates a comparable amount of ALP activity in both strains and thus a comparable amount of stromal cell differentiation into osteoblasts. In contrast, R1 v. P6 data indicates reduced ALP activity in the P6 strain. We therefore conclude: 1) that the reduced BMD found in the P6 strain is not a result of impaired differentiation of bone marrow stromal cells into

osteoblasts but a result of a reduced number of stromal cells, and 2) that the AKR strain may not be a suitable substitute for R1 as the control strain.